DATE: December 02, 2014

TO: Dr. Margo Schwab
Office of Management and Budget
Office of Information and Regulatory Affairs

FROM: National Children's Study Program Office

SUBJECT: Request for Non-Substantive Change to National Children's Study, Neuropsychosocial Generic Clearance (OMB Control #0925-0661, Expiration Date: June 30, 2015) Parental Mental Health Formative Research Project (LOI3-MHLTH-09)

CC: Ms. Seleda Perryman, Ms. Mikia Currie, Dr. Sarah Glavin, Ms. Jamelle Banks

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The National Children's Study (NCS) received a Notice of Action from the Office of Management and Budget (OMB) on November 25, 2013 approving the new generic allocation, A Methodological Study to Assess Mental Disorders for NCS Birth Parents (LOI3-MHLTH-09), under the Neuropsychosocial Generic Clearance (#0925-0661).

The NCS requests a non-substantive change from Office of Information and Regulatory Affairs (OIRA) to reflect refinements made to the previously approved formative research project. Details are provided below.

Collection of Saliva Specimens
We propose to enhance the ongoing Parental Mental Health Study to determine telomere length in as many as 400 of the 1200 study parents and to explore the relationship of telomere length across multiple mental health conditions. This can be accomplished through the collection of saliva samples.

Rationale. In recent years, chromosome telomere length has been identified as a biological marker of cumulative stress and biological aging, and may be as or even more valid than psychological measures. A quick, inexpensive assay for evaluation of chromosomal telomere length using saliva cells is now available. The assay does not involve or rely on analysis of genes but is a measure of the physical length of the ends of chromosomes. For purposes of the NCS that will be following 100,000 kids and their parents for 21 years, the potential value of a simple inexpensive measure of toxic stress and possibly declines in health status that can be collected quickly is immense.

Chromosomes are protected against spontaneous DNA damage and other errors in replication by telomeres, which are caps at ends of chromosomes. With cell replication across the lifespan, telomeres shorten in human somatic cells. Telomere shortening has been observed in association with psychological adversity and other multiple conditions promoting inflammation and oxidation including depression and stress disorders. Research findings in the past year have indicated reduced telomere length in depressed adults, (Wolkowitz, Mellon et al. 2011; Wolkowitz, Reus et al. 2011; Wolkowitz, Mellon et al. 2012) those with traumatic stress disorder (Ladwig, Brockhaus et al. 2013) and individuals exposed to family violence (Drury and Theall 2014; Drury, Mabile et al. 2014).

The NCS requests to explore the value of telomere length as a general indicator of psychological stress based upon a biomarker that could enhance or even replace phenomenologically based mental health screens some of which can be lengthy and burdensome for subjects. Telomere length specimen assays are inexpensive and use saliva or buccal swabs as biological sources.

There is growing evidence that telomere biology may be an important mediator of an individual's health as well as serving as a measurable, valid biomarker of current and future well-being. Investigators have recently documented, for the first time, that telomere length is significantly reduced in placentas from pregnancies complicated by intrauterine growth restriction (Toutain, Prochazkova-Carlotti et al. 2013). In March of 2014, researchers reported that babies born with shorter telomeres appear to be at increased risk for biological processes triggered by genomic instability such as cancer and age-related diseases (Moreno-Palomo, Creus et al. 2014). It is reasonable to hypothesize for future studies that mental health conditions like maternal depression and PTSD mediate the integrity of pregnancy and more distal outcomes like pediatric cancer in the offspring of these mothers and fathers.

Methods. Following consent in the provider location, all participants who consent to have a saliva specimen collected will be asked, at that time, to allow the interviewer to instruct the participant on providing a saliva sample using Orangene (OGR-500) collection tubes. This method for saliva collection has been previously used in the NCS Vanguard Study during pregnancy and birth visits as an alternative to blood collection. The estimated time for saliva collection is 6 minutes, which also includes the time for the interviewer to explain the collection process to the participant as well as the saliva collection. Samples will be transported back to the PMH Study Office for temporary storage until they are shipped for extraction and analysis at an analytical laboratory, at Harvard Medical School's (Partners Healthcare Center for Personal Genetic Medicine Genotyping Facility) which routinely conducts telomere analysis (see Attachment B.12 Saliva Collection and Transport Form).

Saliva collection will be requested for all participants recruited in-person beginning at the time the saliva collection is approved until recruitment is completed. As of 7/21/2014, there are 549 completed interviews. It is projected that recruitment will continue for another 5 to 6 months to recruit sufficient participants to complete 1200 interviews; thus approximately 100 participants will be asked to consent to saliva collection each month. The goal is to have an estimated 400 samples collected for telomere analysis. This is a sample that is larger than many studies on telomeres in mental health and should provide adequate power to detect differences in telomere length. The consent form has been revised to included saliva sample collection (see Attachment B.6 Consent Form Amended).

Upper limit Fifteen percent of all interviews will be selected for validation of completion and quality assurance. Following completion of selected interviews, participants who completed the interviews will be called by study staff and asked a series of questions using a validation script (Attachment B.1 Quality Assurance Interview). The interview will take approximately 5 minutes. Responses will be entered into the REDCap database.

Storage & Handling of Saliva Specimens. Saliva samples will be stored temporarily in a locked storage room at the UMMS Chang Building, 222 Maple Avenue, Shrewsbury until they are shipped for analysis of telomere length to an analytical laboratory. The stored and shipped samples will be labeled with the participant's identification number. No other identifying information will be kept with the samples. The Chang Building is a locked FISMA-compliant building accessible only to authorized persons via a badge swipe or to visitors admitted by authorized personnel. The storage room is accessible only to key study

staff and facilities personnel. Samples will be shipped via FedEx to the analytical lab for analysis. They will be destroyed according to analytical laboratory protocols once the analysis is completed.

Specimen tracking data and analytical results will be entered into the study REDCap database and FoxPro tracking database.

Privacy. With regard to the saliva collection, because genetic information is unique to the individual, there is a small chance that someone could trace research results back to the participant. The risk of this happening is very small, but may grow in the future. There is a federal law called the Genetic Information Nondiscrimination Act (GINA) that, in general, makes it illegal for health insurance companies, group health plans, and most employers, except those with fewer than 15 employees, to discriminate against individuals based on their genetic information. However, it does not protect against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. If participants do not share information about taking part in this study, this risk will be reduced.

IRB Approval: IRB clearance for this activity has been obtained by the local participating field contractor. Please see the amended IRB protocol (Attachment B.1 IRB Protocol Amended) and IRB approval letters (Attachment B.10, B.11).

Data Collection Burden: The NCS is requesting an additional 255 burden hours. The original burden hours approved on 11/25/2013 for this study was 500. If approved, the new total burden hours would be 755.

Estimates of Annual Hour Burden

Data Collection Activity	Type of Respondent	Estimated Number of Respondents	Estimated Number of Responses per Respondent	Average Burden Hours Per Response (in hrs)	Estimated Total Annual Burden Hours
Informed Consent	Pregnant Women and Birth Fathers & Postpartum Parents	1200	1	10/60	200
Specimen Collection – Saliva^	Pregnant Women and Birth Fathers & Postpartum Parents	400	1	6/60	40
Quality Assurance Interview	Pregnant Women and Birth Fathers & Postpartum Parents	180	1	5/60	15
TOTAL		**1200**			**255**

^ The timing of the saliva specimen collection activity is an estimate; the respondent for Attachment B.12 is the data collector and therefore, the timing is not included in the burden.

Annualized Cost to Respondents

Data Collection Activity	Type of Respondent	Estimated Total Annual Burden Hours	Hourly Wage Rate*	Respondent Cost
Informed Consent	Pregnant Women and Birth Fathers & Postpartum Parents	200	$22.01	$4,402
Specimen Collection – Saliva	Pregnant Women and Birth Fathers & Postpartum Parents	40	$22.01	$881
Quality Assurance Interview	Pregnant Women and Birth Fathers & Postpartum Parents	15	$22.01	$330
TOTAL		**255**		**$5,613**

* Based on the mean wages for all occupations. National Compensation Survey: Occupational wages in the United States May 2012, U.S. Department of Labor, Bureau of Labor Statistics.

List of Attachments

B.1 IRB Protocol 07152014 Amended
B.6 Consent Form Amended
B.9 Quality Assurance Interview
B.10 IRB Approval Letter 07222014
B.11 IRB Approval Letter 08092014
B.12 Saliva Collection and Transport Form